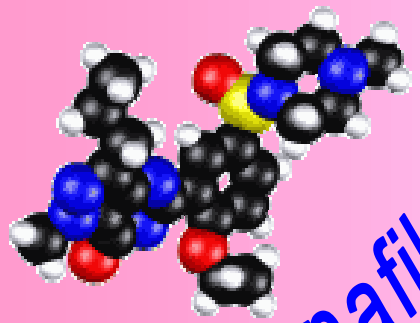
Environmental Aspects of Pharmaceuticals and Personal Care Products



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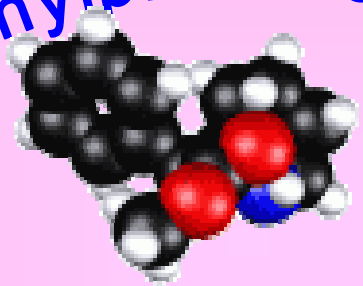

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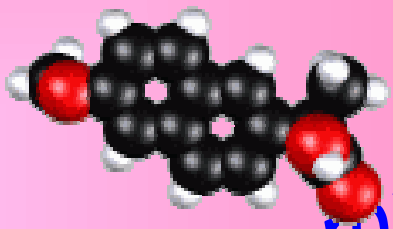

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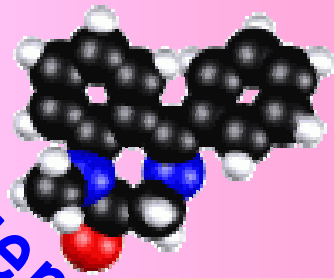

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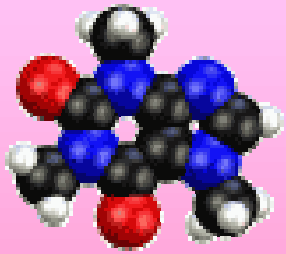

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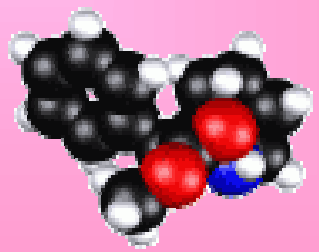

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Pharmaceuticals and Personal Care Products (PPCPs) as Environmental Pollutants

= *Pollution from Personal Actions* <

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U.S. EPA Notice

The U.S. Environmental Protection Agency (EPA), through its Office of Research and Development (ORD), funded this research and approved the materials that formed the basis for this presentation. The actual presentation has not been peer reviewed by EPA.

U.S. EPA, Office of Research and Development
National Exposure Research Laboratory
Environmental Sciences Division
Las Vegas, Nevada

extensive materials available at EPA's **PPCPs web site:**

http://www.epa.gov/nerlesd1/chemistry/pharma/index.htm

Primary Goals of the U.S. EPA's *Office of Research and Development*

- **Identification of potential (future) environmental concerns:** anticipatory research; emerging issues.
- **Proactive vs. Reactive — Pollution prevention vs. remediation/restoration**: Identify and foster investigation of "hidden" or potential environmental issues/concerns before they become critical ecological or human health problems.
- **Ruling-in/ruling-out vs. Uninformed rules:** Provide bases for informed decisions. Ensure that science leads eventual decisions for guidance or to regulate/not regulate.
- **Foster interdisciplinary research & collaboration:** Catalyze research by academe, private sector, government.

American Chemical Society

- Slide Presentation by Christian Daughton: **Pharmaceuticals & Personal Care Products (PPCPs) as Environmental Pollutants**

- Critical Review Article by Daughton and Ternes: **Pharmaceuticals & Personal Care Products in the Environment: Agents of Subtle Change?**
  -- Summary/Background
- Origins and Fate of PPCPs in the Environment
- Use of PPCPs in the Environment as Analytical "Tools"

(Continued)

This web site is a dynamic "work in progress". Much of its content is continually added to and updated as more information becomes available, as more insights are acquired, and as feedback is received. With this in mind, all the information on this site (except that which has been published in the referred literature and that provided by other researchers) should be considered as "draft" and thereby subject to modification. Also note that the thrust of this web site is that of the science associated with the broad topic of PPCPs in the environment. No aspect of the materials provided by EPA employees on this site should be construed as representing thinking or positions regarding policy. This point is codified in the mission of the Office of Research and Development (ORD), which sponsors this web site. ORD is charged with developing the science that may or may not be used in the future by the Agency's regulatory Program Offices and Regions to establish, modify, or carry out national environmental policies. This web site should instead be viewed as a forum or clearinghouse for conveyance of information and opinions with the primary intention of furthering a scientific dialog on the topic of PPCPs in the environment.

http://www.epa.gov/nerlesd1/chemistry/pharma/index.htm

[EPA Home] [ORD Home] [NERL Home] [ESD Home]

Author: Christian Daughton
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Last Updated: 09/05/01

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- concluded -

U.S. EPA STAR Grants

$3M awarded in September 2001

A. Lynn Roberts (Dept. Geography & Environ. Eng., John Hopkins University)

- **Pharmaceuticals and Antiseptics: Occurrence and Fate in Drinking Water, Sewage Treatment Facilities, and Coastal Waters**

Tohren C. G. Kibbey (Dept. Civil Eng. & Environ. Science, Univ. Oklahoma)

- **The Influence of Amphiphilic Molecules on the Environment Fate and Transport of Pharmaceuticals**

Kevin L. Armbrust (Univ. of Georgia - CAES Griffin Campus)

- **The Environmental Occurrence, Fate and Ecotoxicity of Selective Serotonin Reuptake Inhibitors (SSRIs) in Aquatic Environments**

Bruce Brownawell (Marine Sciences Research Center, Stony Brook University)

- **Occurrence and Fate of Pharmaceuticals and Personal Care Products in Groundwater Environments**

David W. Graham; Cynthia Larive (Dept. Environ. Eng., University of Kansas)

- **Fate and Effects of Fluoroquinolone Antibacterial Agents in Aquatic Ecosystems**

Howard S. Weinberg (Dept. Enviormental.Science and Engineering, Univ. of North Carolina at Chapel Hill)

- **Impact of Residual Pharmaceutical Agents and Their Metabolites in Wastewater Effluents on Downstream Drinking Water Treatment Facilities**

“Disclaimers”

PPCPs vs. EDCs Y PPCPs 1 EDCs

- PPCPs and EDCs are **not** synonymous — they are intersecting sets of compounds and toxicological issues.
- Must avoid confusion regarding their relationship.
- Only a small subset of PPCPs are known/suspected of being **direct-acting** EDCs (e.g., synthetic steroids); toxicological concerns usually differ. EDCs comprise members from many disparate chemical classes.

"PBTs" and "POPs" – only one part of the risk puzzle?

During last three decades, the impact of chemical pollution has focused almost exclusively on conventional "priority pollutants"†, especially on those collectively referred to as "persistent, bioaccumulative, and toxic" (PBT) pollutants or "persistent organic pollutants" (POPs).

The "dirty dozen" is a ubiquitous, notorious subset of these, comprising highly halogenated organics (e.g., DDT, PCBs).

The conventional priority pollutants, however, are only one piece of the larger risk puzzle.

† it is important to recognize that the current "lists" of priority pollutants were primarily established in the 1970's in large part for expediency — that is, they could be measured with off-the-shelf chemical analysis technology. Priority pollutants were NOT necessarily selected solely on the basis of risk.

Einstein on: *Environmental Monitoring*

"Not everything that can be counted counts, and not everything that counts can be counted." (oft attributed to Albert Einstein)

corollary for environmental monitoring

Not everything that can be measured is worth measuring, and not everything worth measuring is measurable.

Overview: Pharmaceuticals in the Environment

- Certain pharmaceutically active compounds (e.g., caffeine, aspirin, nicotine) have been known for over 20 years to occur in the environment.
- Environmental occurrence primarily resulting from treated and untreated sewage effluent.
- Only more recently has a larger picture emerged — numerous PPCPs can occur (albeit at very low concentrations).
- Prior discovery delayed primarily by limitations in analytical environmental chemistry (ultra-trace enrichment and detection).
- Domestic sewage is a major source — not just hospital sewage. CAFOs are a major source of antibiotics.

continued -

Overview: Pharmaceuticals in the Environment

- Continual input of PPCPs to aquatic environment via sewage can impart a persistent quality to those compounds that otherwise possess no inherent environmental stability.
- The full extent, magnitude, and ramifications of their presence in the aquatic environment are largely unknown.
- Vast majority of all ecological monitoring studies to date have been performed in Europe.
- Use/release of antibiotics and natural/synthetic steroids to the environment has generated most of the controversy to date, but a plethora of other PPCPs have yet to be examined. Scope of overall issue is ill-defined.

continued -

Overview: Pharmaceuticals in the Environment

- Toxicological significance for both humans and ecological exposure to multiple chemicals at trace concentrations (ppb-ppt) for long durations is poorly understood.
- If PPCPs eventually prove to be an environmental concern, it is unknown whether sewage treatment facilities could be cost-effectively modified to reduce emissions.
- Source control (aimed at both disposal and medical practices) may prove more effective.
- Focus should be on proper and sufficient science for establishing occurrence, exposure, susceptibility/effects, so that sound decisions can be made regarding human and ecological health.

- concluded -

PPCPs as Environmental Pollutants?

- PPCPs are a diverse group of chemicals comprising all drugs (available by prescription or over-the-counter; including the new genre of "biologics"), diagnostic agents (e.g., X-ray contrast media), "nutraceuticals" (bioactive food supplements such as huperzine A), and other consumer chemicals, such as fragrances (e.g., musks) and sun-screen agents (e.g., methylbenzylidene camphor); also included are "excipients" (so-called "inert" ingredients used in PPCP manufacturing and formulation).

- Drugs differ from agrochemicals in that they often have multiple functional groups (many are amphiphilic) and usually have lower effective doses. This complicates fate/transport modeling and lends an extra dimension to the analytical techniques required for monitoring. Also designed for use by/for the individual.

- In contrast to the conventional PBTs, most PPCPs are neither bioaccumulative nor volatile; some, such as the musks, however, do indeed fulfill the criteria for PBTs.

Classes of PPCPs Identified in Environmental Samples

- In addition to antimicrobials and steroids, over 50 individual PPCPs or metabolites (from more than 10 broad classes of therapeutic agents or personal care products) have been identified (up to 1999) in environmental samples (mainly in sewage, surface, and ground waters).

- It is important to note, however, that although a number of representatives from this subset of therapeutic classes have been identified in the environment, members of most classes have yet to be searched for.

continued -

Majority of PPCP classes have no environmental survey data

- Environmental survey data have yet to be reported for many classes (and class members) of PPCPs.
- While the literature is silent regarding these PPCPs, is this because of an absence of data or a failure to report "data of absence"?
- Many of these unreported drugs are among the most widely prescribed in the U.S.

- *concluded* -

“Environmental Surprise”

The concept of "surprise" in environmental systems perhaps originally formalized by the ecologist Crawford S. (Buzz) Holling in the early 1970s. "Surprise" occurs when:

“... causes turn out to be sharply different than was conceived, when behaviours are profoundly unexpected, and when action produces a result opposite to that intended - in short, when perceived reality departs quantitatively from expectation.”

Holling, C.S. 1986. “The resilience of terrestrial ecosystems: local surprise and global change.” In: Sustainable Development of the Biosphere, Clark, W.C. & R.E. Munn (Eds.), Cambridge University Press, Cambridge, UK, 292-313.

"Emerging" Risks

It is reasonable to surmise that the occurrence of PPCPs in waters is not a new phenomenon. It has only become more widely evident in the last decade because continually improving chemical analysis methodologies have lowered the limits of detection for a wide array of xenobiotics in environmental matrices. There is no reason to believe that PPCPs have not existed in the environment for as long as they have been used commercially.

- concluded -

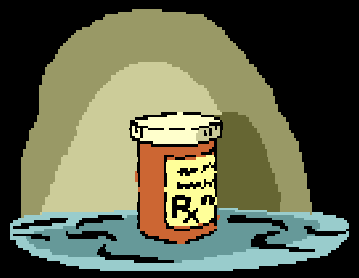
Origins of PPCPs in the Environment

- Portions of most ingested drugs are excreted in varying unmetabolized amounts (and undissolved states, primarily because of protection by excipients) primarily via the feces and urine.
- Other portions sometimes yield metabolites that are still bioactive. Still other portions are excreted as conjugates.
- Free excreted drugs and derivatives can escape degradation in municipal sewage treatment facilities (removal efficiency is a function of the drug's structure and treatment technology employed); the conjugates can be hydrolyzed back to the free parent drug.
- Un-degraded molecules are then discharged to receiving surface waters or find their way to ground waters, e.g., leaching, recharge.

continued -

Inter-Connectedness of Humans and the Environment

- Occurrence of PPCPs in the environment mirrors the intimate, inseparable, and immediate connection between the actions and activities of individuals and their environment.
- PPCPs owe their origins in the environment to their worldwide, universal, frequent, and highly dispersed but cumulative usage by multitudes of individuals.

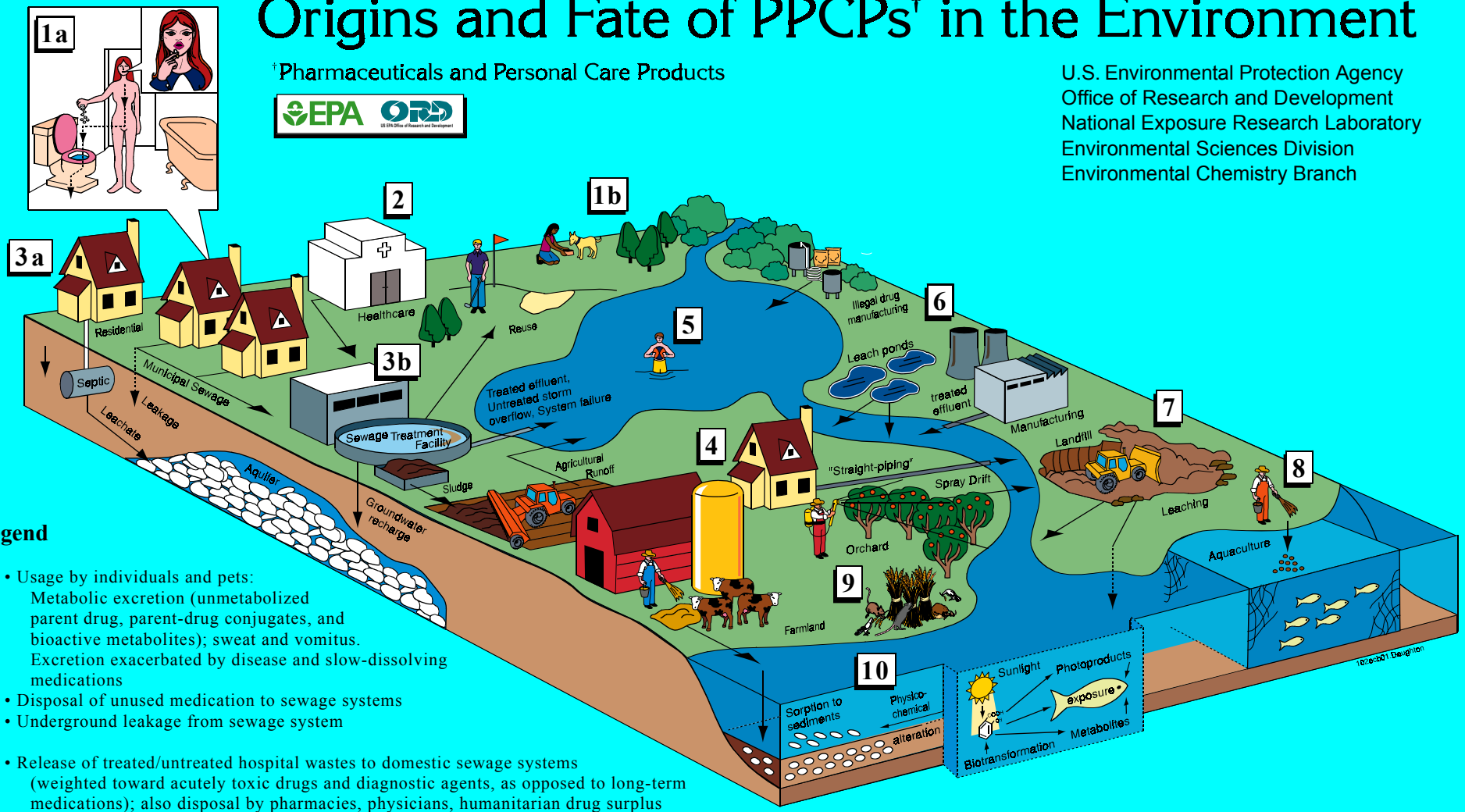


adapted by Daughton from Ternes (April 2000)

Origins and Fate of PPCPs† in the Environment

†Pharmaceuticals and Personal Care Products

U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory
Environmental Sciences Division
Environmental Chemistry Branch



Legend

1 • Usage by individuals and pets:
Metabolic excretion (unmetabolized parent drug, parent-drug conjugates, and bioactive metabolites); sweat and vomitus.
Excretion exacerbated by disease and slow-dissolving medications
• Disposal of unused medication to sewage systems
• Underground leakage from sewage system

2 • Release of treated/untreated hospital wastes to domestic sewage systems (weighted toward acutely toxic drugs and diagnostic agents, as opposed to long-term medications); also disposal by pharmacies, physicians, humanitarian drug surplus

3 • Release to private septic/leach fields
• Treated effluent from domestic sewage treatment plants discharged to surface waters or re-injected into aquifers (recharge)
• Overflow of untreated sewage from storm events and system failures directly to surface waters

4 • Transfer of sewage solids to land (e.g., soil amendment/fertilization)
• "Straight-piping" from homes (untreated sewage discharged directly to surface waters)
• Release from agriculture: spray drift from tree crops (e.g., antibiotics)
• Dung from medicated domestic animals (e.g., feed) - CAFOs (confined animal feeding operations)

5 • Direct release to open waters via washing/bathing/swimming

6 • Discharge of regulated/controlled industrial manufacturing waste streams
• Disposal/release from clandestine drug labs

7 • Disposal to landfills via domestic refuse, medical wastes, and other hazardous wastes
• Leaching from defective (poorly engineered) landfills

8 • Release to open waters from aquaculture (medicated feed and resulting excreta)

9 • Release of drugs that serve double duty as pest control agents:
examples: 4-aminopyridine experimental multiple sclerosis drug → used as avicide; warfarin anticoagulant → rat poison; azacholesterol antilipidemics → avian/rodent reproductive inhibitors; certain antibiotics → used for orchard pathogens; acetaminophen analgesic → brown tree snake control

10 Ultimate environmental fate:
• most PPCPs eventually transported from terrestrial domain to aqueous domain
• phototransformation (both direct and indirect reactions via UV light)
• physicochemical alteration, degradation, and ultimate mineralization
• volatilization (mainly certain anesthetics, fragrances)

Christian G. Daughton, U.S. EPA-Las Vegas

February 2001

http://www.epa.gov/esd/chemistry/pharma/index.htm

Needs and Gaps: PPCPs

Sources/Origins

- Determine relative contributions to environmental loadings from disposal to sewage (and trash) vs. excretion/washing.
- Relative contributions from hospitals vs. municipal sewage.
- Relative contributions from CAFOs vs. human use (esp. antibiotics).
- Relative contributions of illicit vs. licit drugs.
- Possible importance of excipients.
- Need for nationwide database showing prescription, OTC-sales data, and usage (GIS).

Needs and Gaps: PPCPs

Occurrence

- Concentration, frequency, and geographic extent and distribution in sewage and aquatic systems need to be better defined on a national level (more monitoring - surface, ground, drinking).
- Significance of regional prescribing/usage differences.
- Significance of sewage treatment technology capabilities.
- Establish status and trends of individual PPCPs.
- Literature is silent regarding occurrence of many PPCPs. Is this because of an absence of data or a failure to report "data of absence"?

Needs and Gaps: PPCPs

Fate/Transport

- Identify potential for bioactive metabolites and other transformation products.
- Establish major environmental degradation mechanisms (biological, physicochemical).

Needs and Gaps: PPCPs

Hydrology

- Better understanding of transport to and degradation in groundwater.
- Groundwater recharge (accidental and purposeful); significance regarding recycling of contaminants.
- Need for consistent, national guidance regarding composition of active recharge waters. What level of treatment should be required? Tailor to local geology.

Needs and Gaps: PPCPs

Analytical Chemistry

- Need for enrichment and detection methodologies for compounds more polar than environmental chemists are used to dealing with (new approaches such as MIP).
- Facilitate more widespread and efficient implementation of non-target monitoring approaches.
- Importance of establishing a nationwide monitoring network to detect all NEWLY present (emerging) chemicals in waterways (including PPCPs): e.g., “Chemical Fingerprint Anomalies”.

The Imperative for a Nationwide Approach to Identifying Emerging, Nascent Chemical Risks

A proposal is outlined following the end of this presentation for establishing a nationwide monitoring network for detecting all NEWLY present (emerging) chemicals in waterways.

Historical approach to identifying and controlling chemical risks is **reactive**.

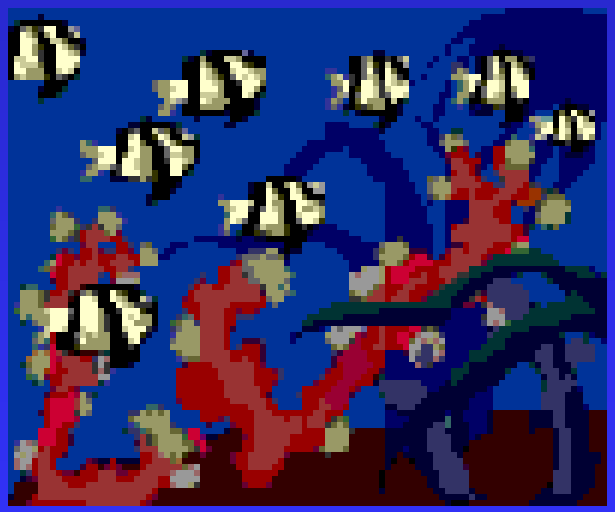
Environmental regulators have traditionally approached chemical pollution by devoting resources solely to managing established, well-characterized risks.

Proactive approach is needed to **preventing** the establishment of new risks so that their management would not be needed.

Needs and Gaps: PPCPs

Exposure

- Determine significance of chronic, long-term exposure via drinking water and foods (fin/shell fish) to multiple chemicals (ng/L concentrations).
- Define the most important therapeutic/use classes (currently most is known only regarding antibiotics and estrogenic steroids).



Needs and Gaps: PPCPs

Toxicology

- Determine importance of efflux pumps as first line of defense for aquatic organisms.
- Expand understanding of non-target effects (esp. for non-target organisms).
- Improve ecotoxicological testing (e.g., accommodate for more subtle effects and endpoints not currently measured; e.g., long-onset, latent damage; subtle shifts in behavior or intelligence).
- Expand ecotoxicological considerations for accommodating MOAs (e.g., angiogenesis inhibitors, efflux pump inhibitors)
- Elucidate importance of low-level effects (e.g., nM-pM, sub-pbb/ppt), hormesis, and paradoxical dose-response.
- Better elucidate multiple effects, additive effects, interactions (synergism/antagonism), exposure duration (e.g., multi-generational), windows of exposure vulnerability, and aggregate, cumulative, complementary exposures.

Subtle (currently unrecognized) Effects:

some examples:

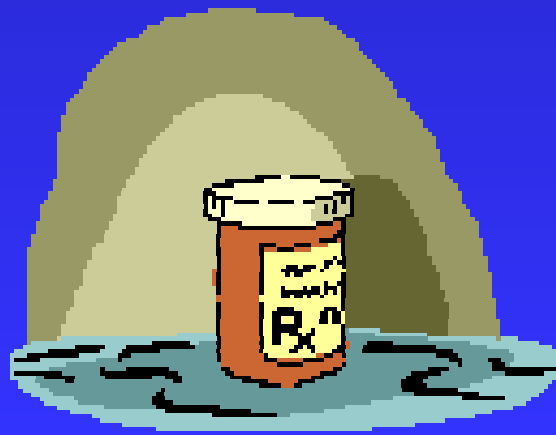
- Profound effects on development, spawning, and wide array of other behaviors in shellfish, ciliates, and other aquatic organisms by SSRI and tricyclic antidepressants.
- Dramatic inhibition of sperm activity in certain aquatic organisms by calcium-channel blockers.
- Antiepileptic drugs (e.g., phenytoin, valproate, carbamazepine) have potential as human neuroteratogens, triggering extensive apoptosis in the developing brain → neurodegeneration.
- ppm and sub-ppm levels of various drugs (NSAIDS, glucocorticoids, anti-fibrotics) affect collagen metabolism in teleost fish, leading to defective/blocked fin regeneration
- Multi-drug transporters (efflux pumps) are common defensive strategies for aquatic biota — possible significance of efflux pump inhibitors in compromising aquatic health?

continued -

Needs and Gaps: PPCPs

Medical

- Individualization of therapy (e.g., proactive "calibrated dosing" to minimize dosing).
- Minimize overuse, misuse, imprudent use (involves patient education as well). Antibiotics are a MAJOR concern with respect to selection of resistant species (with profound human health and ecological ramifications).
- Expand exploration of non-chemical alternatives to traditional medications (e.g., reducing/eliminating drug dosages by use of placebos).



Needs and Gaps: PPCPs

Design/Manufacturing

- Aim for "environmental friendliness" (green design and innocuous fate).
- Accelerate development of better drug-delivery systems and formulations (e.g., inhalable, dermal, to minimize dosage).
- Accelerate development of enantiomeric drugs.

Needs and Gaps: PPCPs

Engineering

- Delineate the factors that determine the susceptibility of PPCPs to biological sewage treatment.
- Develop inexpensive alterations to sewage plant treatment technologies to control refractory PPCPs.
- Ensure that RO for groundwater recharge is reliable (and then treating the rejected brine for enriched contaminants).

Needs and Gaps: PPCPs

Control

- Disposal: Standardized set of national regulations for disposal of unwanted, expired PPCPs (public, state, and medical, e.g., nursing homes, physician samples).
- Implement "Extended Producer Responsibility" (EPR) (e.g., manufacturers and distributors).
- Outreach efforts for heightening public awareness for recycling alternatives (e.g., reverse distributors).
- Source separation for domestic wastes: New technologies for dealing with waste at the source (e.g., separation of streams). Toilet re-engineering is but one example.
- Continue nationwide elimination of straightpiping and septic systems; also overflow events.

Needs and Gaps: PPCPs

Prevention

- Proactive vs. Reactive.
- Encouragement for purchase of only needed amounts of PPCPs (e.g., package sizes conducive to avoiding expiration).
- Reduce over-dispensing and black market sales of drugs (e.g., “Internet pharmacies”).
- Expand use of “drug mining” (e.g., hospital reclamation of highly toxic drugs from excreta and other wastes).
- Expand use of “reverse distributors”.

Needs and Gaps: PPCPs

Risk Assessment/Regulation

- Impart better understanding that traditional assessments accommodate only a small portion of the universe of chemicals to which humans and organisms are exposed.
- Chemical stability is not a prerequisite to establish a "persistence" in the environment.
- Accumulate occurrence data for CCL (Contaminant Candidate List).
- Ensure that new knowledge is assimilated in new regulations.
- Evaluate the Precautionary Principle.

Needs and Gaps: PPCPs

Public Outreach

- Recognition that POPs and PBTs represent only a portion of the overall pollutant load.
- Show the health benefits of minimizing overuse/misuse of drugs (e.g., antibiotics).
- Capitalize on occurrence/effects issues to increase public understanding and appreciation for environmental science. Tie actions of the individual to environmental consequences.
- Create materials for public education (esp. via the web).
- Use of drug monitoring to raise community awareness of local usage (esp. illicit/abused drugs).
- Use of drug monitoring to raise community awareness of inadvertent financial support to terrorism.

Needs and Gaps: PPCPs

Research Planning/Catalysis

- Catalyze and promote further exploration, discussion, and collaboration on emerging pollutants by all stakeholders.
- Develop formal interagency workgroup to develop cohesive plan for PPCPs (and emerging pollutants).
- Organize national/international conferences devoted to specific issues under the overall topic.

Proposal: Interagency Strategy for "Emerging Contaminants"

Development of Interagency Emerging-Contaminants Research/Monitoring Strategy

PPCPs provide opportunity for science community to be proactive/collaborative.

Need to coordinate activities from wide array of government agencies, public entities, private organizations, and other stakeholders. Accommodate varied interests and perspectives.

Ultimate Objective: Design and implement an early warning system for any new chemical contaminant – whether naturally occurring or anthropogenic.

Near-Term Objective: Develop cohesive, unified strategy for determining risks of ambient PPCPs to wildlife and humans.

Near-Term Implementation: ***2002 Workshop on PPCPs***. Senior science representatives and central coordinators from major federal entities, including CDC, DOI (USFWS), EPA, FDA, NIH, and USGS. Later workshops would involve other entities, such as states, public/private granting organizations, manufacturers/distributors, regulators.

Workshop Product: ***Framework for Development of a National PPCPs Coordination Strategy.***

Questions?

feel free to contact:

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http://www.epa.gov/nerlesd1/chemistry/pharma/index.htm

The Imperative for a Nationwide Approach to Identifying Emerging, Nascent Chemical Risks

- Chemicals that have not previously existed in the environment, but which are just beginning to develop or "emerge," present unknown risks, some of which cannot be anticipated.
- Historical approach to identifying and controlling chemical risks is **reactive**.
- Environmental regulators have traditionally approached chemical pollution by devoting resources solely to managing established, well-characterized risks.
- **Proactive** approach is needed to **preventing** the establishment of new risks so that their management would not be needed.
- New and unanticipated chemicals (together with their transformation products) that have not previously occurred in the environment need to be identified as early as possible — **well before their becoming pervasive in the environment**.

- continued

One Proposal for a Nationwide Approach to Identifying Emerging, Nascent Chemical Risks

"Pollutant Fingerprint Anomalies"

(C.G. Daughton, 29 August 2001)

- Develop repertoire of highly reproducible chromatographic/ electrophoretic separations methods coupled with a sensitive, universal detector (e.g., any of various mass spectrometric formats).

- Periodically screen aqueous samples from nation-wide locations (representative of urban, rural, and pristine areas) for existence of any NEW constituent – ignoring all those that are normally present (a type of "chemical amnesty" for the purposes of focusing resources on new pollutants).

- Approach would require sample-concentration schemes capable of multi-orders-of-magnitude "enrichment" of solutes, regardless of their polarities. The organic constituents in the resulting extracts would then be subjected to appropriate separation schemes, yielding reproducible "fingerprints" that reflect the compounds present and their relative abundances.

- continued

"Pollutant Fingerprint Anomalies"

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- The resulting separation "fingerprints" would be generated using software/firmware that controls for relative retention, using various internal standards. The fingerprints would be continually interpreted by newly developed software designed to search for and detect (1) "aberrant" abundance ratios of existing components, and (2) "new" components. The latter would include those chemicals in previously unoccupied retention windows as well as those having anything less than perfect co-elution with pre-existing compounds.

- Such an approach using "**fingerprint anomalies**" would give the ability to detect chemicals that are just beginning to find their way into the environment – including transformation products that could not be easily predicted even if the chemical were known before hand.

- Once suspected new anomalies are detected, more resource-intensive efforts could be devoted to (1) identifying their chemical structures, and (2) if the anomaly indeed proved to be an emerging, nascent chemical, the appropriate toxicological studies could be initiated together with identification of source and establishment of control measures, if warranted.

- concluded -

The "Risk Cup": Complex and Currently Unresolvable Issues Affecting Regulatory Approaches Aimed at Multiple Exposure / Multiple Effects (graphically summarized on following slide)

Multiple effects (endpoints): Exposure to one chemical having multiple mechanisms/modes of action (MOAs)

Interactions — Synergism/Antagonism: Unanticipated endpoints (deviating from additive, or no-interaction) from interactions of multiple chemicals

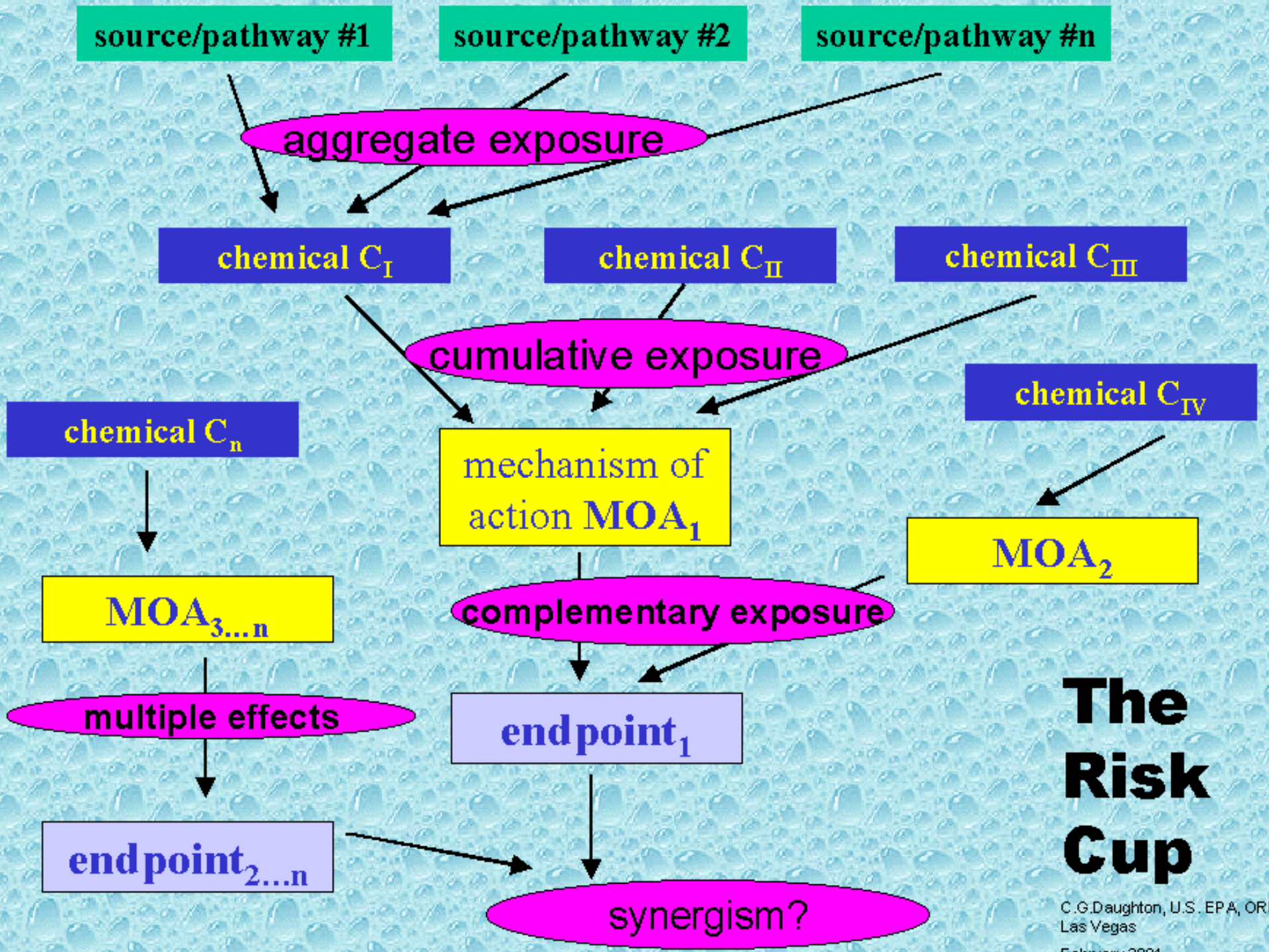
Aggregate Exposure: Factoring additive exposure via all pathways and sources for one chemical (cumulation of individually smaller risks); e.g., antibiotics via food residues and drinking water

Cumulative Exposure: Factoring exposure to multiple chemicals sharing a common MOA; e.g., anticholinergics, selective serotonin reuptake inhibitors, calcium channel blockers

Complementary Exposure: Co-exposure from chemicals acting by different MOAs but yielding similar ultimate endpoints; e.g., all types of antidepressants

Biological Effects of Low-Level Exposure (BELLE): For example, **Hormesis** – paradoxical or unanticipated effect at low doses of a chemical (see: http://www.belleonline.com/)

Ultimately, *regulatory decisions are not solely a matter of science* – they must also factor in complex, interacting societal values


source/pathway #1
source/pathway #2
source/pathway #n
aggregate exposure
chemical C_I
chemical C_{II}
chemical C_{III}
cumulative exposure
chemical C_n
chemical C_{IV}
mechanism of action MOA_1
MOA_2
$MOA_{3...n}$
complementary exposure
multiple effects
$endpoint_1$
$endpoint_{2...n}$
synergism?
The Risk Cup
C.G.Daughton, U.S. EPA, ORD/NERL, Las Vegas
February 2001

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Multiple exposures to same PPCP

single PPCP:
e.g.,
tetracycline

aggregate exposure

Water (contaminated from excrement)
Food (inadvertent drug residues)
Medication

Exposure to multiple PCPPs sharing same MOA

multiple PPCPs, same sub-class:
e.g., SSRIs

cumulative exposure

common, shared MOA
e.g., via serotonin modulation

Exposure to multiple PCPPs sharing same end effect

multiple PPCPs, unrelated sub-classes:
e.g., antibiotics

complementary exposure

different MOAs
e.g., all resulting in inhibition of microbial growth

Exposure to multiple PCPPs resulting in interactive effects

multiple PPCPs, unrelated classes:
e.g., SSRIs & MAOIs

combined exposure

different effects
e.g., resulting in synergism/antagonism